THE ENTRY OF GENETICS INTO MEDICINE

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I have been asked to recount the history of the invasion of genetics into medicine. The scope of this history is too broad, so I have chosen to tell that which I believe to be the heart of the matter, that from which it seems to me all else flows. It is my view that what genetics has done for medicine is to give it a coherent core. Whatever kind of doctor one is, when we see a patient, we are seeing someone whose biological individuality is at odds with the conditions of life.

This history is encapsulated in changes in ideas. One of these ideas is the reduction of phenotypes to molecules, made possible by technology suitable to the ideas. A reciprocal idea is the gradual liberation of human genetics from the thought and terminology of drosophila genetics. Not that the reductive path was possible without drosophila genetics. Nothing could be done without it, but as medical missions were increasingly better served by the reductionist path, drosophila thinking got in the way. This shift in thought began in earnest around 1950, when the reductionist path entered an exponential phase of growth that it has pursued ever since. Perhaps genetics has changed medical thinking most notably in its focus on molecular individuality. The biological uniqueness of each person is reflected in the expression of disease, and I would add at the outset, that individuality was nowhere to be seen or heard in the drosophila lexicon.

Why should we care about history? Is it not enough simply to observe how genetic thinking has altered that of medicine? History, however, is not just chronology; it is a way of thinking. The historian Carl Schorske calls it "thinking with history."[1] "If we locate ourselves in history's stream," he says, "we can begin to look at ourselves—as conditioned by the historical present as it defines itself out of, or against, the past." In the medical context, this means that we

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cannot define this transformation of medicine except historically. The thoughts of today always are compounded of those of the past.

Thinking with history is not new in medicine. Medicine is a historical subject. Every encounter begins with history: first, that of the present illness, then that of past illnesses, and finally, that of the health careers of relatives. In pathogenesis, we are moving further and further back in the lifetime, finding the precursors of disease in childhood, infancy, or even *in utero*. Nor is that the end. Today we inquire into the possession of genes that may represent risk of some kind, and then we ask which parent they came from and about ethnicity, knowing the variable genetic composition of cultural, endogamous groups. The elucidation of pathogenesis is incomplete until we know the exact sequence of base pairs in the offending allele or alleles, which leads us back into phylogeny and evolution. Indeed, the story of evolution is recounted in changes in the qualities, frequencies, and distribution of genes; so, one of the most evident signs of the invasion of genetics into medicine is the necessity to analyze a patient's illness in three time frames at once: that of phylogeny, that of ontogeny, and that of the experience of the moment. Evidently, one of the benefits of this incursion of genetics into medicine is to cause the physician to "think with history."

There is another reason for pursuing this history and for teaching it to medical students. Teaching how to do things, diagnosis and treatment, for example, is training, while teaching how and why things got that way, the ideas of medicine, is education. Medical education necessarily includes both. We want the doctor to proceed according to well-tested paths in diagnosis and treatment, but it is a grasp of why those paths exist that makes him or her a physician rather than an artisan. It is in refining the theoretical and philosophical framework of our understanding that we justify and perpetuate the standing of medicine in the university.

At the center of the history of genetics is the definition of the gene.[2] Each new definition could be made only on the basis of the last; each was necessary to the next. For example, there was no point in asking how genes functioned until there could be some sense of how they were related to their phenotypes. So, each new definition provided answers to outstanding questions and made it possible to ask new ones, the answers to which led to yet another definition. With each of these, the field of genetic interest broadened and became more inclusive, embracing biochemistry and molecular biology, immunology, anthropology, evolutionary biology, and disease. It will be seen that, in all of the definitions, the gene's unitary relationship to its product is preserved.

At first, the gene itself was at the center of explanations of disease, but today

in medicine, we are more likely to conjure with its product in its role as a unitary step, or element, of one among the many homeostatic devices that preserve the integrity of open systems moving freely in an indifferent environment. One outcome of this examination of progress in the definition of the gene is a continuing refinement in the biochemical and molecular definition of human individuality. Since the ultimate virtue of genetics in medicine is the discovery and description of individuality in disease, these serial definitions of the gene parallel our dissection of that individuality.

So, the definition of the gene will be the central thread of my story, which will recount the reduction of phenotypes to those protein unit steps of homeostasis. This molecularization of biology will illuminate the history of three other threads: (1) the relationship of disease to natural selection and evolution, (2) how our understanding of the interactions of the protein gene product with experiences of the environment has brought the concept of heritability to the fore with its advancement of the logic of prevention, and (3) how the synthesis of genetic and medical thought has brought medicine new obligations to patients and their families, as well as to the society that supports it. These threads, too, respond to changes in the definition of the gene, and in the end, all come together to form a fabric for medical thinking, a much-needed centripetal force to counter the powerful centrifugal scatter of reduction.

Mendel's gene and that of its rediscoverers were defined statistically; there was no sense of actual entity. After about 1915, however, the drosophilists described the gene as a unit of segregation and recombination, that is, a unit implied by the results of matings. It also was described as a unit of mutation and of function. It was a convenient definition, expressing a very direct one-to-one relationship between gene and phenotype, but nothing at all was known about what it was that segregated or about mutation other than that it is correlated with phenotypic variation. Nor was anything known about what transpired between the gene and its phenotype. The drosophila genetics enterprise, with its operational definition of the gene, existed until the 1940s in a kind of airtight compartment that could be refined and expanded without reference to the outside. It was independent of the actual nature of the gene it defined, as well as of its function.[3] As the only game in town, it made the rules and contributed the lexicon for the genetics of other organisms, including that of *Homo sapiens*. For medicine, the operational definition made it possible to make sense of family aggregation and, in giving the disease under study a mode of inheritance as dominant, recessive, or sex linked, it gave information useful to patients. But before the 1950s, genetics had little impact on medicine.[4,5]

Still, this elucidation of the physical basis of heredity was essential for the next step, which was to define the gene according to function. This occurred in the 1940s in the work of Beadle and Tatum, which culminated in the one gene–one enzyme hypothesis.[6] Now, the operationally defined gene, still an abstraction, could be said to work by specifying an enzyme that was responsible in some way for the relationship, also one to one, of the gene to its phenotype. This characterization of gene function, and the one-to-one principle, stimulated a return to Archibald Garrod's inborn errors of metabolism, first described in 1902.[7] It is certainly thinking with history when we compare the meaning of those words today with the meaning at the time of their origin. Then, inborn error of metabolism meant a hereditary loss of an enzyme that compromised a metabolic step. Today, the words evoke (a) the biology of reproduction by which traits are said to be inborn, (b) the limitless range of mutation, and (c) the impact of genetic variation on the integrated physiological apparatus that maintains the integrity of open systems. It is clear that Garrod perceived something of the sort; he suggested from the beginning that there would be very many more such inborn errors, so many and of such frequency as to constitute a chemical individuality expressed in the uniqueness of each human being.

The period of the 1940s and 1950s saw a confluence of genetic, biochemical, and medical ideas that brought about the transition in human and medical genetics from a drosophila-like version to human biochemical genetics. That is, in describing pathogenesis of disease, physicians' attention by then had passed from the organ to the cell, and advances in biochemistry revealed the details of intracellular events: enzymes, energy transfer, biosynthesis and degradation, and so on.[8] So, the functional definition of the gene was the signal for the description of new inborn errors to enter an exponential rate of increase in number that continues to this day, a rate of accretion fueled from the 1950s to the present by public support of biological science, itself an offshoot of the successes of physics during World War II. An immediate outcome was the rediscovery of inborn errors by biochemists, who found them in the course of investigating enzyme pathways. Glucose-6-phosphatase deficiency in glycogen storage disease[9] was discovered by Cori, and galactose-1-phosphate uridyltransferase was shown to be deficient in galactosemia by Isselbacher et al.,[10] both without reference to Garrod. Similarly, Pauling failed to cite Garrod when he differentiated sickle cell hemoglobin from the normal. Pauling proposed that sickle cell disease be perceived as a "molecular" disease, a label that lost out in the competition with inborn error of metabolism,[11] but again thinking with history, we see molecular disease as an adumbration of future emphasis on molecules in the description

of both genes and their protein products, with special significance for the concept of the individuality of disease.

The recognition of biochemical genetics as an opportunity for careers brought investigators to the field to start a new specialty of medical genetics, with clinics created to care for "genetic" diseases and administered in divisions belonging to departments, usually of pediatrics, but also of internal medicine and obstetrics. Occasionally, the administrative unit was a department. By 1975, there were 16 departments of medical genetics in American medical schools and more than 75 divisions.[12] Today, nearly every school has at least a division of medical genetics. This expansion was accompanied by the founding in 1947 of the American Society of Human Genetics by drosophila geneticists of great percipience, who saw that if human genetics were ever to thrive, it needed physicians who knew genetics and geneticists who knew human biology.[13] Two years later, there was an *American Journal of Human Genetics*, a quarterly with perhaps 400 pages per volume. Now, it appears monthly, there are two volumes per year, and each volume includes about 1500 pages. There are many other genetics journals here and abroad, as well as other societies. The medical genetics enterprise is still growing in both number and scope, having moved from monogenic disorders to the elucidation of the genetic basis of cancer, malformations, and other diseases of complex origin that constitute the principal bane of human health.

The functional definition of the gene also had a strong influence in releasing the drosophiline constraints on the concepts, and so the language, of medical genetics.[14] Heterozygous expressions were found of genes that, in homozygotes, caused recessive diseases. Evidently, there were hierarchies of gene action between the protein presumed to be its product and the disease phenotype, inner expressions of genes unknown to the drosophilists. So, dominance and recessiveness were seen to be properties not of the genes, but of their products, and words like penetrance and expressivity, useful when the phenotype is visible to the eye, but less meaningful at the biochemical level, began to fade. The classical example of the awkwardness of drosophiline locutions, cited almost immediately, was the sickle cell phenomenon, a recessive when viewed as a disease, but a dominant when the sickled cell was the phenotype. Then, when hemoglobin S was shown to differ from hemoglobin A in electrophoretic mobility, a new word, codominant, was employed. Further, another ambiguous usage, that of intermediate dominance, had to be used when the two phenotypes, sickle cell disease and sickled cells, were compared because the latter was perceived to be intermediate to both homozygotes. Accordingly, we began to refer more frequently to the biochemical reality, omitting words suitable only for abstractions.

Perhaps the most significant contribution of the era of the functional gene for medicine was the reality of the protein, whether an enzyme, hemoglobin, or other, that bore a relationship to a single gene. The gene itself was still an abstraction, but we are concerned here with medicine; for medicine, with its need to unravel pathogenesis, the fact that gene products were enzymes, for example, had greater meaning than the identification of the genetic material and the description of the gene. It was this that promoted the exponential discovery of new inborn errors, not the double helix. But neither could the observation of the one-to-one relationship alone precipitate the action. It was biochemistry, then approaching its heyday, that furnished the stimulus. Every laboratory had charts of biochemical pathways, cascades, cycles, and integrated systems, and all were mediated by proteins, mostly enzymes. So, for the first time, it was possible to conceive of an inborn error for every enzyme or other protein, to see how the loss of any one in a pathway could cripple the whole physiological unit to cause the accumulation of intermediate metabolites, as well as the absence of those beyond the block, and to give body, if only in the imagination, to Garrod's principle of chemical individuality. If there was variation in any or all of the proteins in the pathway or other device, then molecular individuality would be ensured. Developments in molecular genetics often are proclaimed to be "revolutionary," and so, no doubt, they are, but to my mind the revolution of genetics in medicine began with the functional gene with its one-to-one relationship of gene to protein because it is the protein product that determines the functional efficiency of homeostasis. So, at the beginning of the pathogenesis of all, or nearly all, diseases is the variant protein gene product. Of course this, concept was expressed only in relation to monogenic disorders, but even in the 1950s, there was the dim, inchoate notion that multifactorial diseases would be explained also by variant proteins, however strong the role of the environment. After all, Fisher had shown in 1918[15] that the genes for continuously distributed qualities were the same as those that produced segregating phenotypes, and as the decades passed, the idea took form that any and all disease would be explained by some incongruence between a variant homeostasis and experiences of the environment. In this way, the protein unit step came gradually to occupy its central position in our concepts of disease and molecular individuality. Surely we are thinking with history when we scan the lists of variants in *Mendelian Inheritance in Man*, the inborn errors in the *Molecular and Metabolic Basis of Inherited Disease*, and the rosters of genes implicated in atherosclerosis, diabetes, and hypertension.

The 1950s were also a defining moment in what some would say were more

important ways. The paper of Avery, McLeod, and McCarty, revealing DNA as the genetic material, appeared in 1945, and that of Watson and Crick came to light in 1953. The cracking of the code and descriptions of transcription and translation followed, and in the 1960s Yanofsky demonstrated the colinearity of sequence of the base pairs in DNA with the amino acids in proteins.[16] This represented a new structural definition of the gene as determiner of the specificity of the protein unit step of homeostasis, and mutations now could be demonstrated and their clinical expression described. Later, in the 1970s and 1980s, the discovery of restriction enzymes made it possible to isolate fragments of genes, which could be sequenced with implications for, say, an antenatal diagnosis that could be made without clinical or biochemical detail.[17]

The realization that gene variants could be inferred from protein differences stimulated efforts to determine the extent of genetic variation in the human and other species, observations of great significance to population geneticists and, as it happened, also to medicine. Two studies, carried out with neither knowing of the other, revealed that the structural variation in soluble enzymes of both *Homo sapiens* and *Drosophila melanogaster* was the same.[18,19] Variants were found in frequencies of 1% or more at about 30% of the loci. This means that each individual person or fly is heterozygous at 7–10% of the loci. Such loci were called *polymorphic*; similar polymorphic variation has been found in hundreds of species, so it is a phenomenon of life.

This work was done in the 1960s and 1970s, and it stirred a controversy in which the question was argued whether or not such a degree of frequent variation could be maintained in any species by natural selection. Finally, it was agreed that it could not, and that such frequencies of polymorphic alleles could be attained by chance alone. At first, these controversies seemed to be of interest only to population geneticists, but as time passed, polymorphic proteins began to turn up in association with disease, especially multifactorial disorders, so that by the 1980s, some were said to be risk factors. Now, if genes are involved in rheumatoid arthritis, atherosclerosis, and diabetes, as they most certainly are, they must be frequent since the diseases are common. So, the conclusion is inescapable that some common genes, however they have attained their frequencies, are harmful in some people and under some conditions. This has turned out to be a concept to conjure with in medicine, an idea that has moved slowly, almost imperceptibly, to become the basis for new thinking. It was through monogenic diseases that genetics was introduced to medicine in the 1950s and 1960s, while the concept of polymorphism, expanding slowly through subsequent decades, has made genetics central to our thinking about all disease. How this

occurred emerges in the description of the other threads of this history. We have not yet finished defining the gene. I should add here that we will not finish it until the fruits of the genome project are in and have been collated, correlated, integrated, and understood.

Many people thought that the structural gene was definitive, but almost immediately it was clear that there was more. For example, there were bits of DNA that seemed to control transcription, but were not reflected in translation. Then, introns and exons were described, so a new molecular definition emerged that included all transcribed DNA plus some nontranscribed controlling elements.[20]

This exposure of the details of DNA advanced the cause, principally of the biologists, but there were new ideas for medicine, too. For example, gene action could be described without the use of drosophiline language. One such usage, gene-environment interaction, was shown clearly to be a misrepresentation since the interaction is always between the environment and the proteins that are the engines of the cell. The genes, in contrast, are passive, requiring aggregations of proteins, called by some protein machines, to accomplish transcription, which they do in response to signals transduced by proteins from outside stimuli. So, here is additional support for the idea of the protein gene product as the central feature of the cell in both health and disease, and in medicine. The protein is assuming gradually the position once occupied by the genes. It is not that the concept of the gene is in any way devalued; it is only that, in medicine, when we look for explanations of disease, we find them in their variant protein products. It is the proteins that integrate and cooperate to attain states of congruence with the environment or incongruence, which in the absence of some kind of compensation, must lead to disease. Finally, exposure of the molecular structure of the gene has made it possible to use linkage, an old idea, to locate genes in the chromosomes, to visualize their sequences, and to give them identity. The benefits of linkage analysis date at least to the 1940s, when Haldane suggested that linkage with a known phenotype, say a blood group, could detect the asymptomatic carriers of the genes for Huntington's disease; in the ensuing decades, methods for such exercises were devised. The tempo of such work increased markedly in the 1990s, when linkages of disease-related genes were discovered, at first monogenic, but increasingly in diseases of complex origin, too. It is interesting that, although the technology for finding linked genes is infinitely superior to that of 40 years ago, the principles are the same, and we find a return to such drosophiline concepts as penetrance, laid to rest in the 1950s and 1960s when it became possible to show biochemical effects in hetero-

zygotes. Still, the use of the linkage principle has opened the genome to examination at all points, and as everyone knows, in a few years we shall have a map of the whole complement of human genes, itself a first step to a molecular description of all disease.

EVOLUTION

Each definition of the gene helped to illuminate the processes of evolution. In the 1930s and 1940s, the operational gene was the instrument for a synthesis of genetic and evolutionary thinking called neodarwinism. We already have seen the implications for evolution of the structural gene in polymorphism, and the interpretations of evolution as molecular change were given a further boost by the description of the molecular gene.

For medicine, two aspects of evolution stand out. First, the exposure of the details of DNA in the molecular gene reinforced the idea that the origins of disease reside in incongruence between products of the DNA that reflect the variations in those details and the conditions to which open systems must adapt. Those variations are the mutants that a species needs to be adaptive, so disease is a by-product of evolutionary necessity. Second, to evolutionary biologists, natural selection is that which leads to adaptation. That which removes whatever is disadaptive is "purifying," a word they use without the irony any physician sees. To the evolutionary biologist, there is a discontinuity; to us there is none. To us, a gene product may contribute positively under one condition and otherwise under another. This is part of our dilemma in the ethics of disease prevention.

HERITABILITY

A third thread is heritability, a locution suitable for the operational gene. It is an expression of the degree to which the variability in a phenotype expressed in a population is determined by genetic differences. In human genetics, it has been used in demonstrating a genetic element in diseases of complex origin. For example, a heritability of 0.5 often was cited to show that type 1 diabetes is no less an "inherited" property than a product of the "environment." Obviously, the usefulness of this concept declined as the qualities of the gene were bared, and we learned to expose individuality at the molecular level. But, recently, the idea has reappeared in a new guise.[21] A measurement of heritability in a population is based on correlation within families for phenotype; those who lack the trait do not enter in. Now, however, we know that there may be many in a population who are genetically vulnerable, but do not have the disease, whether due to a lack of exposure to some provocation or to variability in the genetic

susceptibility. So, when the environmental pressure is heavy, all degrees of vulnerability are likely to succumb, but when it is light, fewer exhibit the disease or, when there is none, those who show symptoms are those with the most disruptive mutants and who need no such stimulus. When the provocation is heavy, the heritability is said to be low; when light, high.

This seems to me to be an important concept for medicine. Let us take as one example, lung cancer. A few cases are familial, but most are not; most are smokers, so we would say the heritability is low. At present, the incidence of lung cancer is decreasing, but we do not expect it to disappear even if no one smoked; there are those familial cases. So, we might say that the heritability of lung cancer is increasing. Rickets is another example. Here, a simple treatment cured or prevented most cases, leaving only a few monogenic forms of resistant rickets. Again, the heritability rose. So, a prime contribution of genetics to medicine lies in the exposure of genetic vulnerability and prevention of disease. In a word, we seek to raise the heritability to as near 1.0 as possible. Perhaps, in time, prevention will assume the primacy now given to treatment.

ETHICAL ISSUES

The final strand in this tapestry is that of the contribution made by genetics to the socialization of medicine, which as late as 1950, was a largely autonomous enterprise deeply engaged with disease and the people who suffered it, but little concerned with their social lives. In the 1960s, however, informed consent became an issue, and other rights were pressed. Medical genetics contributed to this awakening because, by the 1970s, it became evident that knowledge of one's disease-related genes could compromise not only self-image, but also one's role in life; job opportunities could be reduced, or the chance for insurance could be impaired.[22] Further, genetics was applied to antenatal diagnosis, which sometimes meant abortion of diseased fetuses, forcing moral choices on those who underwent the procedure and angering those to whom it is in religion unacceptable—with occasional lethal outcomes to some physicians. Overriding all is public ignorance of genetics and its meaning in their lives, a need partially met by training a cadre of genetic counselors. Philosophical battles raged as early as the 1960s, when ethicists and philosophers became concerned about cloning of people, and there were fears of resurgence of eugenics and the like, questions for which there were no answers then, nor are there many more now. Perhaps the iffiest boon of all is in the use of knowledge of possession by individuals of genes for vulnerability, often of polymorphic frequency, that have a promise of disease that varies from a few percent to certainty. Those are probabilities that,

as everyone knows, mean little to the individual to whom the reality is unknown. This ambiguity will increase as the fruits of the genome project come to light. If we are to reduce this uncertainty, we will need better knowledge of both provocations and of individual development in relation to specific alleles and diseases. Alternatively, we offer a prevention in which relief and anxiety are commingled.

CONCLUSION

Finally, thinking with history, we can see emerging from the swirl of 50 years of experiment, observation, and analysis a new conceptual basis for medical education and practice; the threads of history come together to form a coherent tapestry. The gene and its product take the most prominent position. It is the products that integrate to constitute the means to maintain an open system, and the variations in those proteins that make each unique. It is the genes, however, that bind the individual to the species and to all life; through their powers, both permissive and constraining, they initiate a trajectory of development, maturation, and aging, which although subject to modification by experiences all along the way, preserves the identity of the individual throughout life.

In medicine, we perceive the body as a machine that breaks from time to time, and so we ask the questions: What disease am I facing, and how do I treat it? The disease is treated; the individuality of the person is ignored. When looking at medicine through a genetic lens, however, other questions clamor for answers. Why do we have disease at all, and what forms can it take? Who is likely to be sick, in what way, and when in the lifetime? Beyond these, how can I restore this person to his/her unique steady state? Or, preferably, how can I help this person to skirt the traps laid for him or her in the unique path of life set by the genes, development, and a unique set of experiences? The answers to these questions have been exposed in the history we have examined. We have disease because, as a species, we must have variety and because some of it is certain to be at odds with a culture that is evolving, too. Its forms are determined by the particularity of the variable unit steps of homeostasis and their roles in differentiated cells through development, maturation, and aging. Who will be at risk is a consequence of who has the variable protein product and the relevant experiences and how both came to the affected person. When in the lifetime is determined by development and exposure to provocations and by a gradient of selective effect in which selection is most intense early in life and least at its end. When we observe patients in the context of this logic of disease, such is the complexity of cause and response that each arrives at his or her disease by a different path.

No doubt the historian of 20 or 30 years from now will see today's marvels as merely dim flashes of insight into the reality of a later time. But, thinking with history, it will be plain that the trajectory for the wonders of that reality was set in our time.

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